Scientific Issues in the Regulatory Assessment of Ethylene Oxide Cancer Risk

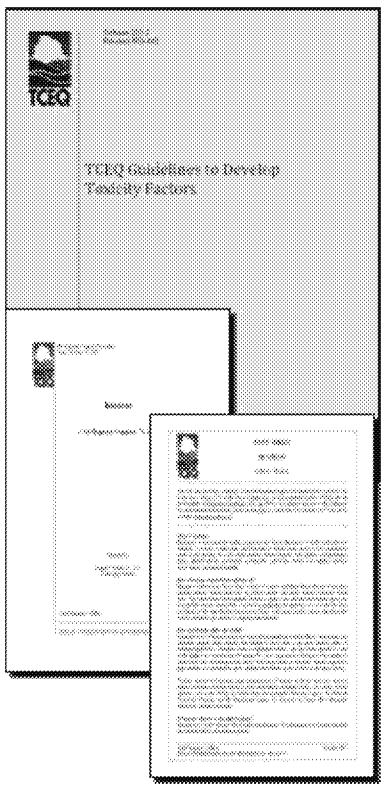
Toxicology, Risk Assessment, and Research Division
Texas Commission on Environmental Quality

6th Semi-Annual
Medical Device Sterilization Conference
October 29-30 | Alexandria, VA

TCEQ Toxicology, Risk Assessment, and Research Division

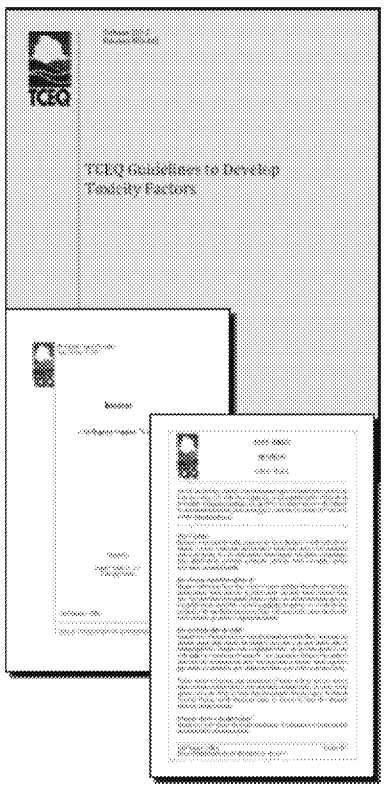
- ≈17 busy, hard-working toxicologists/risk assessors
- Support most programs at the TCEQ
- For example, involved in:
  - ✓ Review of air data from the most extensive ambient air monitoring network in the nation, ≈95 air toxics sites (e.g., VOCs, PAHs, metals, carbonyls, H_2S).
  - ✓ Air permitting (TCAA requires all sources and emissions be authorized, even BBQ pits and water heaters).
  - ✓ Remediation risk assessment.
  - ✓ Risk communication (legislature, public, management, media).
  - ✓ Objective data analysis for policymakers.
  - ✓ *Toxicity factor development (e.g., EtO and CrVI URFs).*

TCEQ Toxicity Factor Guidelines



- Guidelines were originally drafted in 2005
- External expert peer reviewed
- 2 rounds of public comment
- Finalized in 2006
- Updated version was drafted in 2011
- Also subjected to external expert peer review and public comment
- Finalized October 2012
- Both times the external review was organized by Toxicology Excellence for Risk Assessment (*TERA*) with diverse external experts from government (e.g., USEPA, CalEPA), academia (e.g., UC, NYUSM, UTSPH), consulting (e.g., David Gaylor, Bruce Allen, John Christopher), and others (e.g., Lovelace Respiratory Research Institute, NUATRC).
- Updated again in 2015 (323 page guidance document).
- *Our Goal: a state-of-the-science guidance document.*

Some Peer Reviewer Comments



"To the best of my knowledge, this guidance is complete and thorough, even exhaustive, in its coverage of relevant guidance on development of toxicity criteria available in the United States and Europe."

"This draft guidance is not just comprehensive, it is encyclopedic."

"The authors of this report are to be commended for the thoroughness, accuracy and usefulness instilled into this report."

Sound Science

- Our goal: Use state-of-the-science guidelines to derive scientifically-sound toxicity factors.

- Derivations can be found in Development Support Documents (DSDs) available on the web (https://www.tceq.texas.gov/toxicology/dsd/final.html).

- TCEQ has also published various derived values in the peer-reviewed scientific literature (e.g., 1,3-butadiene, nickel, arsenic, cadmium, CrVI, diethanolamine).

Sound Science

A bibliography of some papers by TCEQ toxicologists that have appeared in scientific journals:

1. Nancy B. Beck, Richard A. Becker, Neeraja Erraguntla, William H. Farland, Roberta L. Grant, George Gray, Christopher Kirman, Judy S. LaKind, R. Jeffrey Lewis, Patricia Nance, Lynn H. Pottenger, Susan L. Santos, Stephanie Shirley, Ted Simon, Michael L. Dourson. 2016. Approaches for describing and communicating overall uncertainty in toxicity characterizations: U.S. Environmental Protection Agency's Integrated Risk Information System (IRIS) as a case study. Environment International 89–90: 110–128.

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Open access: http://www.tandfonline.com/eprint/8SbFyWjzj4SPbje53BxP/full

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4. Erraguntla, N.K., R.L. Sielken, C. Valdez-Flores, and R.L. Grant. 2012. An updated inhalation unit risk factor for arsenic and inorganic arsenic compounds based on a combined analysis of epidemiology studies. Regulatory Toxicology and Pharmacology 64: 329–41.

5. Ethridge, S., Bredfeldt, T., Sheedy, K., Shirley, S., Lopez, G., and M. Honeycutt. 2015. The Barnett Shale: From problem formulation to risk management. Journal of Unconventional Oil and Gas Resources 11: 95-110.

6. Goldstein, B.D., B.W. Brooks, S.D. Cohen, A.E. Gates, M.E. Honeycutt, J.B. Morris, T.M. Penning, J. Orme-Zavalets, and J. Snawder. 2014. The role of toxicological sciences in meeting the challenges and opportunities of hydraulic fracturing. Toxicological Sciences 139(2): 271–83

7. Goodman J.E., Sax S.N., Lange S., and L.R. Rhomberg. 2015. Are the elements of the proposed ozone National Ambient Air Quality Standards informed by the best available science? Regulatory Toxicology and Pharmacology 72(1): 134–40.

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9. Grant, R.L., R.J. Rodriguez, C.S. Hofelt and L.C. Haws. 2002. Shortcomings in USEPA approach for predicting risk due to consumption of animal food products impacted by air emissions from hazardous waste combustion facilities: A case study involving phthalates, Human & Ecological Risk Assess. 8: 1137–54.

10. Grant, R.L., V. Leopold, D. McCant, and M. Honeycutt. 2007. Spatial and temporal trend evaluation of ambient concentrations of 1,3-butadiene and chloroprene in Texas. Chemico-Biological Interactions 166: 44–51.

11. Grant, R.L., B.J. Kadlubar, N.K. Erraguntla, and M. Honeycutt. 2007. Evaluation of acute inhalation toxicity for chemicals with limited toxicity information. Regulatory Toxicology and Pharmacology 47: 261–73.

12. Grant, R.L., J. Haney, A.L. Curry, and M. Honeycutt. 2009. Development of a unit risk factor for 1,3-butadiene based on an updated carcinogenic toxicity assessment. Risk Analysis 29: 1726–42.

13. Grant, R.L., J. Haney, A.L. Curry, and M. Honeycutt. 2010. A chronic reference value for 1,3-butadiene based on an updated noncancer toxicity assessment. Journal of Toxicology and Environmental Health, Part B, 13: 460–75.

14. Grant, R.L., A.F. Jenkins. 2015: Use of In Vivo and In Vitro Data to Derive a Chronic Reference Value for Crotonaldehyde Based on Relative Potency to Acrolein, Journal of Toxicology and Environmental Health, Part B, DOI: 10.1080/10937404.2015.1081574.

15. Grant, R.L., S. Taiwo, and D. McCant. 2015. Assessment of chronic inhalation non-cancer toxicity for diethylamine. Inhalation Toxicology DOI: 10.3109/08958378.2015.1103338.

16. Haney, J.T. 2016. Historical drinking water contamination at Camp Lejeune: Regulatory risk assessor and personal perspectives. Human and Ecological Risk Assessment: An International Journal. Human and Ecological Risk Assessment: An International Journal 22:4, 1029-1035.

17. Haney, J.T. 2015a. Use of dose-dependent absorption into target tissues to more accurately predict cancer risk at low oral doses of hexavalent chromium. Regulatory Toxicology and Pharmacology 71: 93-100.

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20. Haney, J.T., T. Phillips, R.L. Sielken, and C. Valdez-Flores. 2015. Development of an inhalation unit risk factor for isoprene. Regulatory Toxicology and Pharmacology 73: 712-725.

21. Haney, J.T., N. Erraguntla, R.L. Sielken, et al. 2012. Development of a cancer-based chronic inhalation reference value for hexavalent chromium based on a nonlinear-threshold carcinogenic assessment. Regulatory Toxicology and Pharmacology 64: 466–80.

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Sound Science

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25. Kirman, C.R., and R.L. Grant. 2012. Quantitative human health risk assessment for 1,3-butadiene based upon ovarian effects in rodents. Regulatory Toxicology and Pharmacology 62: 371–84.

26. McCant, D., S. Lange, J. Haney and M. Honeycutt. 2017. The perpetuation of the misconception that rats receive a 3–5 times lower lung tissue dose than humans at the same ozone concentration. Inhalation Toxicology DOI: 10.1080/08958378.2017.1323982.

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30. Phillips, T.D., S.E. Ethridge, and R.L. Grant. 2011. Practical Implementation of the threshold of concern and NOAEL-to-LC50 ratio factor approach to determine acute effects screening levels. The Toxicologist, Tox. Sci. (Suppl. 2), 120: Abstract No. 1523.

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33. Shaw, B.W., Lange, S.S., and M.E. Honeycutt. 2015. "Lowering the Ozone Standard Will Not Measurably Improve Public Health." Environmental Manager, May issue, pp. 26-31.

34. Haney, J.T., D. McCant, R.L. Sielken, C. Valdez-Flores, and R.L. Grant. 2012.Development of a unit risk factor for nickel and inorganic nickel compounds based on an updated carcinogenic toxicity assessment. Regulatory Toxicology and Pharmacology 62: 191–01.

Sound Science Objectively Reviewed

- Ontario, Canada Ministry of Environment (MOE):
  - ✓ *Deemed the assessment of 1,3-butadiene published by the TCEQ as the most scientifically-sound* after reviewing chemical assessments from Health Canada and Environment Canada, the Province of Quebec, the USEPA, the Swedish Institute of Environmental Medicine, the United Kingdom, and the World Health Organization (WHO), and the States of Louisiana, Massachusetts, Michigan, Minnesota, New Jersey, New York, Ohio, North Carolina, California, and Texas.

Sound Science Objectively Reviewed

- Peer Reviewers on USEPA's Proposed Mercury Air Toxics Standards (MATS) Rule in regard to nickel:
  - ✓ "*I would recommend using the TCEQ URE*...The risk assessment leading to the derivation of this number was performed recently, included an updated and critical review of the literature, and appears to be comprehensive with an emphasis on health protection."
  - ✓ "*Use the TCEQ URE*...This approach: (1) uses human data for the risk estimate, (2) takes advantage of a nickel-exposed cohort (Grimsrud 2003) for which there are data on the prevalence of smoking."
  - ✓ USEPA's independent experts recommended they use our nickel URF.

Sound Science Objectively Reviewed

- The Risk Assessment Specialty Section of the Society of Toxicology (SOT) recognized two of our 2015 papers on CrVI at the 2016 SOT conference as among the top 10 risk assessment application papers of 2015…

Regulatory Toxicology and Pharmacology 71 (2015) 93–100

Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

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Use of dose-dependent absorption into target tissues to more accurately predict cancer risk at low oral doses of hexavalent chromium

J. Haney Jr.

Texas Commission on Environmental Quality (TCEQ), Austin, TX, United States

Regulatory Toxicology and Pharmacology 73 (2015) 834–852

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Consideration of non-linear, non-threshold and threshold approaches for assessing the carcinogenicity of oral exposure to hexavalent chromium

J. Haney Jr.

Texas Commission on Environmental Quality (TCEQ), Austin, TX, United States

Sound Science is Needed for EtO

- TCEQ's EtO assessment is still draft.
- It has undergone a public comment period.
- The agency received numerous comments from diverse groups, both for and against (e.g., NGOs, academia, industry, citizens, first author of USEPA's assessment through another institution).
- After some revisions to the draft, it will also undergo an external scientific peer review by independent experts.

Sound Science is Needed for EtO

- Medical sterilant, chemical intermediate (C_2H_4O)
- Recent USEPA (2016) unit risk factor (URF) is primarily driven by lymphoid cancer, although breast cancer is also included (Marsh et al. 2019 meta-analysis breast cancer RR of 0.97 [0.80-1.18], consistent with no elevated breast cancer risk from EtO).
- USEPA acceptable excess risk range is 1E-06 to 1E-04:
  - 1E-06 excess risk air concentration = 0.1 ppt (0.001 ppb)
  - 1E-05 excess risk air concentration = 1 ppt (0.001 ppb)
  - 1E-04 excess risk air concentration = 10 ppt (0.01 ppb)
- Background ≈55-165 ppt (> USEPA's maximum acceptable)
- Also produced endogenously in the body due to oxidation of ethylene (C_2H_4); mean EtO background in nonsmokers equivalent ≈1.9 ppb in air.
- 2016 NATA – EtO becomes new national risk driver due to URF

Sound Science is Needed for EtO

Sterigenics – Willowbrook, IL:

- February 15, 2019 – State of Illinois issued a seal order against Sterigenics.
- March 29, 2019 - Illinois Department of Health found elevated cases of Hodgkin's lymphoma among women, a cancer type not included in USEPA's URF.
- June 21, 2019 – Illinois passes Public Act 101-0022 regulating EtO emissions from medical sterilizers.
- July 17, 2019 – Consent order between Illinois and Sterigenics (99.9% stack control efficiency or 0.2 ppm).

Sound Science is Needed for EtO

Sterigenics – Smyrna, GA:

August 7, 2019

Cobb Leaders Join Smyrna Effort to Test Air Near Sterilization Plant
An Oversight Committee will seek experts to do independent testing

Smyrna, GA - August 6, 2019 | Cobb County leaders say they'll accept an invitation from Smyrna's mayor to join an effort to conduct independent air testing near a medical sterilization plant in District 2. Smyrna Mayor Max Bacon asked County Manager Rob Hosack and Commissioners Bob Ott and Lisa Cupid to join an Oversight Committee that will include residents, business leaders and others from both the city and county.

The effort comes after a report raised concerns about Ethylene Oxide released from the Sterigenics Plant off Atlanta Road. The EPA considers Ethylene Oxide a cancer-causing chemical, but Georgia's Environmental Protection Division has said Sterigenics is "in compliance with current federal requirements for control of ethylene oxide emissions."

"We need to make sure the community is protected, that people are safe," said Mayor Bacon. "The key is getting this going, getting the air tested and see where we go from there."

Sound Science is Needed for EtO

Some other sites:

- Viant Medical – Grand Rapids, MI
  - Closing "voluntarily".
  - Michigan Department of Health and Human Services - The results of the cancer analyses for the area do not suggest that further investigation is needed.
  - Statistically *decreased* breast cancer (included in USEPA URF).
- Terumo BCT – Lakewood, CO
  - Background ≈ 140 ppt (14× USEPA's maximum acceptable)
  - Colorado Department of Public Health and Environment - No actual increase in lymphoid or breast cancers in the neighborhood.

Sound Science is Needed for EtO

An exploratory example for Texas:

- Highly-industrialized Jefferson County has more EtO emissions on a square mile basis than any other county in Texas (1.1E-02 tons/square mile) with over 300 times more than the US at large (3.5E-05 tons/square mile).
- The incidences of leukemia, non-Hodgkin's lymphoma, and breast cancer are *lower* in Jefferson County than in the general US population.
- In fact, breast cancer incidence is *statistically significantly lower* in Jefferson County compared to both Texas and the US, despite EtO emissions that are 60 times higher than Texas at large and 307 times higher than the US.
- Based on USEPA's 2016 assessment, the exact opposite of this reality would be expected.

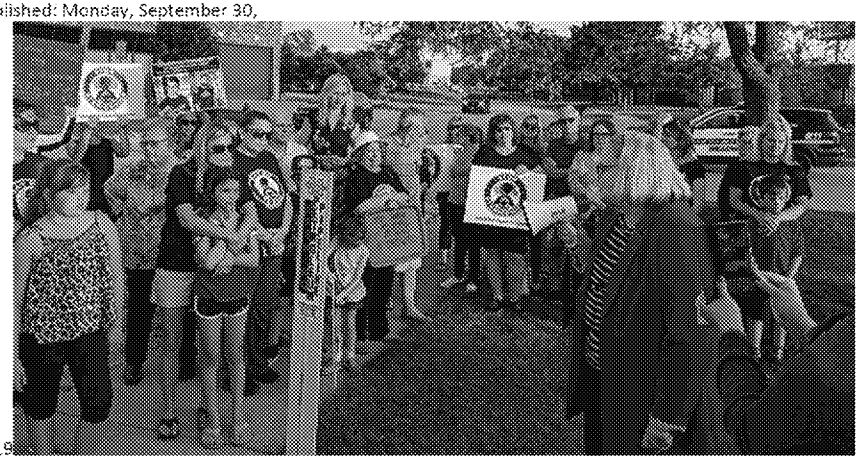
Sound Science is Needed for EtO

- Recent TCEQ work on the EtO carcinogenic dose-response is important and timely work…

2 Chicago plants shut down amid cancer concerns

Sean Reilly, E&E News reporter

Published: Monday, September 30, 2019



Protesters outside a Sterigenics International LLC facility. Image: Sterigenics/Twitter

- Some objective perspective based on best available science would be beneficial to both the public and public officials here (more later).

Sound Science is Needed for EtO

- Here as well…

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Hazardous Air Pollutants: Ethylene Oxide

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Fact Sheet: EPA Taking Steps to Address Emissions of Ethylene Oxide

Latest National Air Toxics Assessment Shows Potential Long-Term Health Concerns in Some Areas

Print the Fact Sheet

- Download and print a copy of this fact sheet in PDF format

OVERVIEW

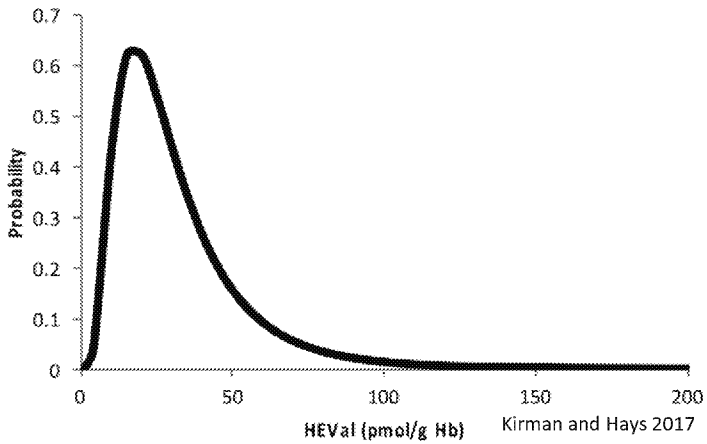
- **AUGUST 22, 2018 --** The U.S. Environmental Protection Agency (EPA) is taking steps to address emissions of the chemical *ethylene oxide* from some types of industrial facilities across the country.
- EPA is addressing ethylene oxide based on the results of the latest National Air Toxics Assessment (NATA), which identified the chemical as a potential concern in several areas across the country. NATA is the Agency's nationwide air toxics screening tool, designed to help EPA and state, local and tribal air agencies identify areas, pollutants or types of sources for further examination.
- The 2014 NATA uses emissions data from the latest National Emissions Inventory (2014 is the most recent data available), along with the latest scientific information on air toxics and health, to estimate long-term air toxics exposures and potential public health risk in census tracts across the United States.

Sound Science is Needed for EtO

- These ill-founded concerns about the carcinogenic risk posed by EtO do not stem from EtO's carcinogenic potency, but rather USEPA's scientifically flawed assessment of it (USEPA 2016).
- The USEPA (2016) URF for EtO is based on a scientifically unjustified, unconventional overall supra-linear dose-response model that has been demonstrated by the TCEQ to be (1) statistically significantly over-predictive; and *not* supported by: (2) carcinogenic mode of action (MOA); (3) data on endogenous levels normally produced within the human body; (4) reality checks on population background incidence; or (5) even appropriate standard model fit criteria.

Sound Science is Needed for EtO

- If USEPA's selected assessment were accurate:
  - Every exposure group in the key NIOSH worker study, even the lowest exposed group, would have statistically increased lymphoid cancer but did not (i.e., non-Hodgkin's lymphoma, MM, lymphocytic leukemia).
  - The air concentration at the maximum acceptable excess risk (0.01 ppb at 1E-04 risk) would correspond to an internal dose almost 40 times lower than even the 1st percentile of normal background EtO levels in the human body…

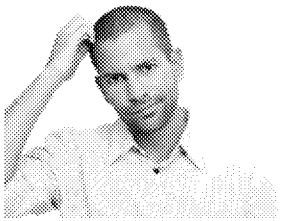


Kirman and Hays 2017

  - Put another way, air concentrations corresponding to more than ≈0.5% percent of mean normal background levels in the human body would result in unacceptable risk.

Sound Science is Needed for EtO

- If USEPA's selected assessment were accurate:
  - The lymphoid cancer background rate *would have to be higher than it actually is* just to accommodate the background incidence *predicted by USEPA's model based on background EtO levels in the human body alone,* much less other potential causes (e.g., without contributions from EtO in ambient air, chance, other leukemogens, etc.).



  - Human data alone would be sufficient to classify EtO as carcinogenic to humans, given the large populations of workers historically exposed to very high long-term levels, but are not (e.g., over 17,000 NIOSH cohort workers in 13 sterilizing facilities historically exposed to up to 77 ppm, millions of times higher than USEPA-cited central tendency ambient levels; if EtO were a potent carcinogen, with about twice the cumulative exposure as the NIOSH cohort, there certainly would be no lack of EtO-induced cancers in the UCC worker cohort, but there is such a lack).
  - Mean environmental concentrations of *ethylene* in many areas would also result in unacceptable risk, and *the average amount of ethylene in your own breath would be over ≈60 times higher than the maximum considered safe*.

Sound Science is Needed for EtO

- For reasons discussed on previous slides, the TCEQ had a scientific and public duty to review all relevant data and conduct a dose-response assessment of its own.
- In doing so, the TCEQ addressed the various scientific shortcomings of USEPA's 2016 assessment (e.g., inappropriate dose-response model selection, flawed AIC and p-value calcs.).

Sound Science is Needed for EtO

- In contrast to USEPA's assessment, the TCEQ's dose-response assessment is supported by:
  - Carcinogenic MOA;
  - Model predictions of the underlying cohort data;
  - Data on normal endogenous levels/biological plausibility considerations;
  - Background incidence/mortality reality checks; and
  - Appropriate standard model fit criteria.

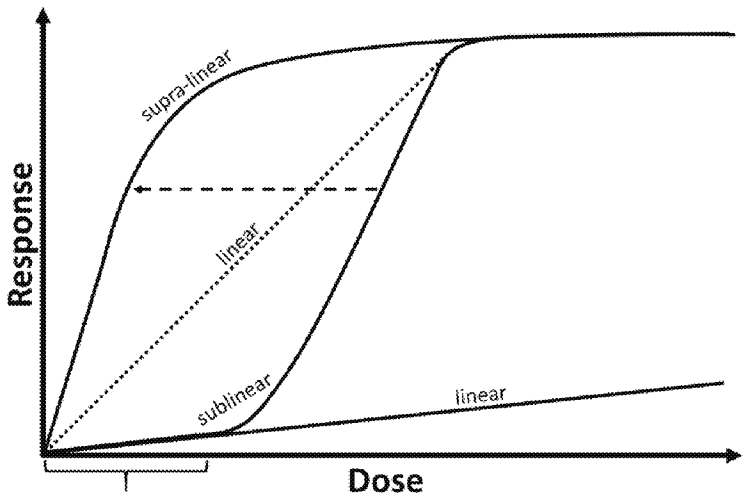
Sound Science is Needed for EtO

- Other regulatory agencies or programs also have a duty to duly and objectively consider these data that inform and support the TCEQ's dose-response assessment as both biologically plausible and the most scientifically defensible available before using any EtO URF (from TCEQ or USEPA) to estimate excess risk or take significant regulatory action.

- https://www.tceq.texas.gov/toxicology

Sound Science is Needed for EtO

- Both the TCEQ and USEPA used results from the same NIOSH cohort (e.g., 17,500+ workers, 53 lymphoid cancer cases), but in different dose-response models:
  - USEPA used an unconventional Two-Piece Spline Model – however, the agency acknowledges *there are no MOA data that support its overall supra-linearity* (i.e., no MOA data support its biological plausibility), and that *sublinearity* is actually expected in the endogenous range (more later).



Sublinearity expected in the endogenous range (as opposed to a steep low-dose slope from an overall supra-linear model), but in the absence of truly low-dose data and dose-response data only being available in the higher-dose region, the full dose-response would not be apparent and the dose-response would shift to the left, with only the portion defined by higher-dose data being defined and appearing supra-linear in nature.

Sound Science is Needed for EtO

- TCEQ used a Cox Proportional Hazards Model – a standard dose-response model; its linearity across EtO doses of interest supported by the mutagenic MOA determined by both agencies (i.e., it is much more biologically plausible).

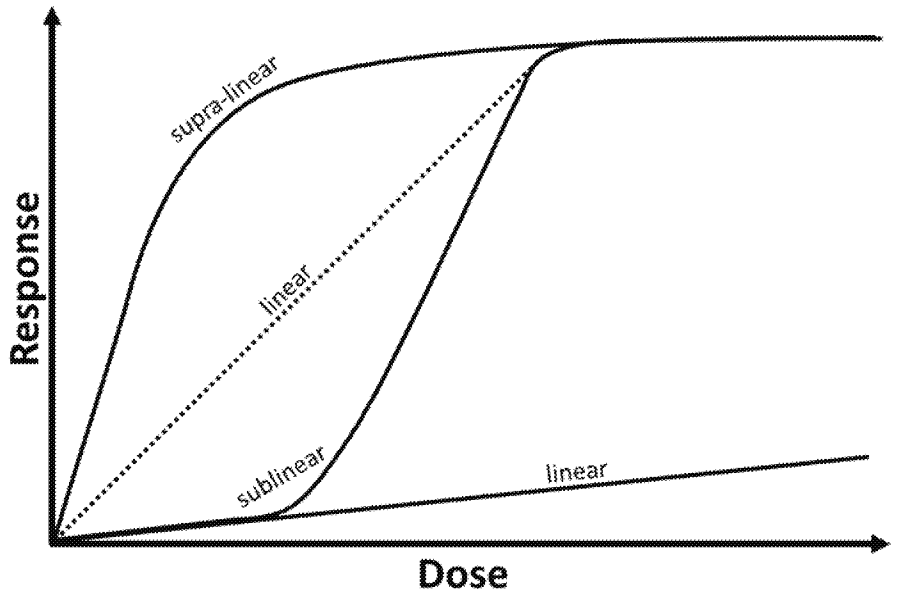
- USEPA also miscalculated model selection criteria (e.g., AIC and model fit p-values) and visually misrepresented model fit to the data, whereas the TCEQ did not.

Sound Science is Now Available for EtO

- The TCEQ's EtO dose-response assessment is supported by:
  - Carcinogenic MOA;
  - Model predictions of the underlying cohort data;
  - Data on normal endogenous levels;
  - Background incidence/mortality reality checks; and
  - Appropriate standard model fit criteria.

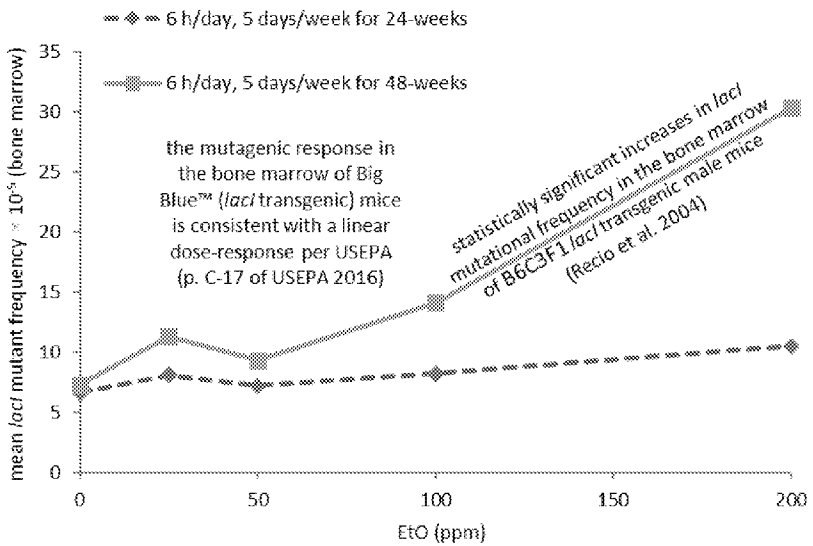
Carcinogenic MOA

- Evidence indicates that mutagenicity is the carcinogenic MOA for EtO, which supports the *standard dose-response model* used by TCEQ as opposed to the unconventional overall supra-linear dose-response used by USEPA (2016).



Carcinogenic MOA

- Since lymphoid cancer drove their carcinogenic assessment, perhaps the most relevant mutagenicity data discussed by USEPA (2016) was that in the bone marrow of mice exposed to EtO by inhalation *in vivo* (Recio et al. 2004), which *USEPA indicates is consistent with a linear dose-response.*



Carcinogenic MOA

- Using supra-linear exposure-response models can only be justified if there is sufficient biological or mechanistic data to support their application.

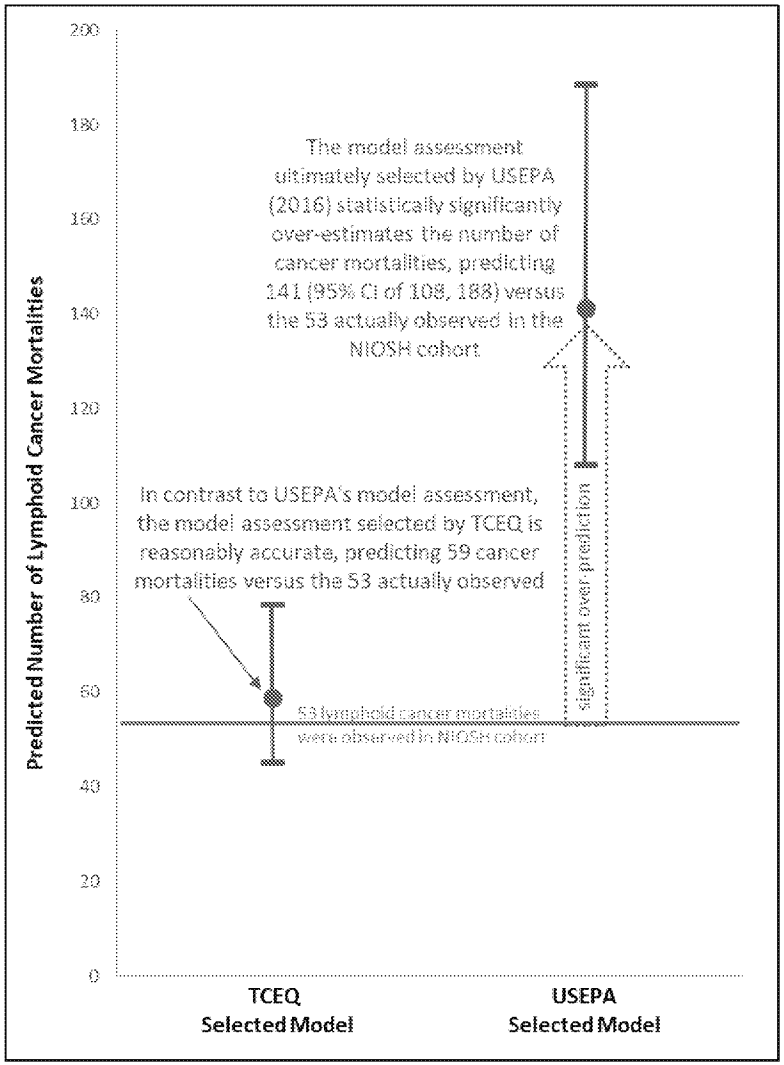
- *USEPA acknowledges* that reasons (biological, mechanistic, or otherwise) supporting a supra-linear dose-response are unknown, stating to their Science Advisory Board "*the EPA is not aware of a mechanistic explanation*" (p. I-29 of USEPA 2016; also see pp. I-34 and 4-71).

Carcinogenic MOA

- As carcinogenic MOA information does not support USEPA's unconventional, overall supra-linear dose-response model, it is not all that surprising that their selected model assessment (i.e., two-piece spline model, UCL) *statistically significantly over-predicts lymphoid cancers* in the very worker dataset that the model is supposed to accurately describe.
- *By contrast*, as the TCEQ used a standard dose-response model consistent with available MOA information, *the TCEQ's selected model assessment* (i.e., Cox proportional hazards, UCL) *accurately describes the underlying lymphoid cancer data…*

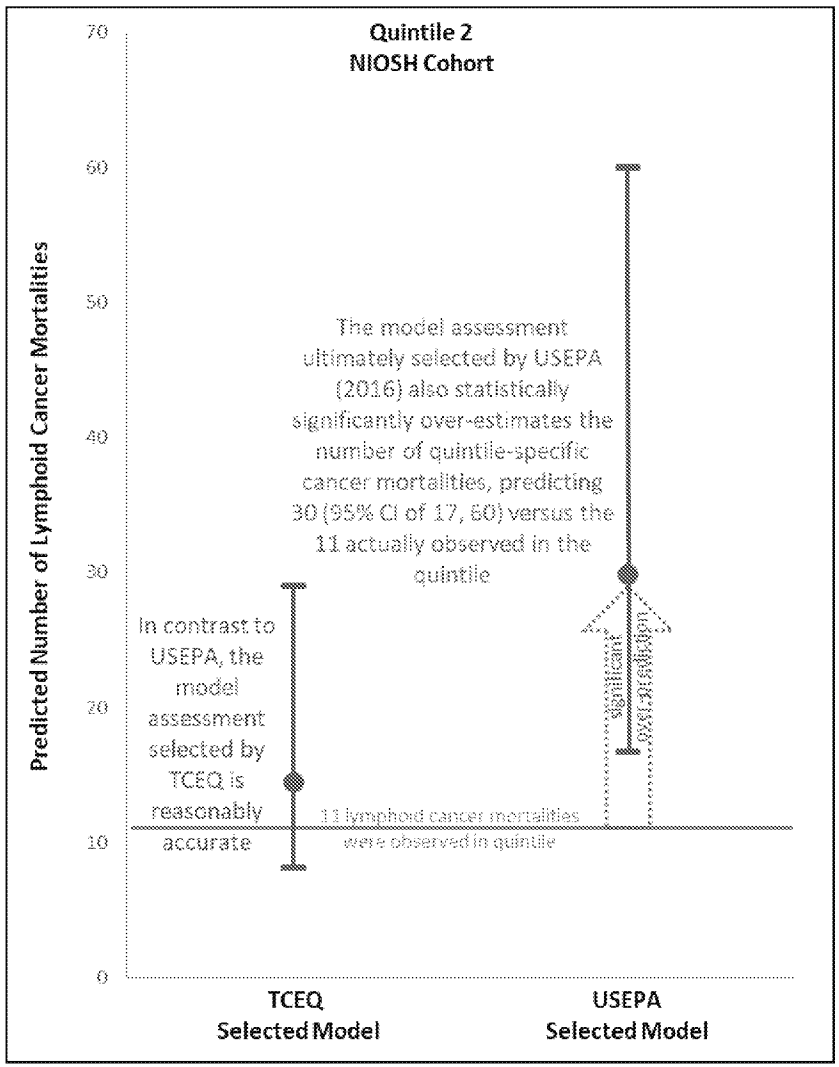
Model Predictions of the Key Data

- For the key NIOSH worker data, *USEPA's selected model assessment statistically significantly over-predicts lymphoid cancers* while TCEQ's model is relatively accurate…



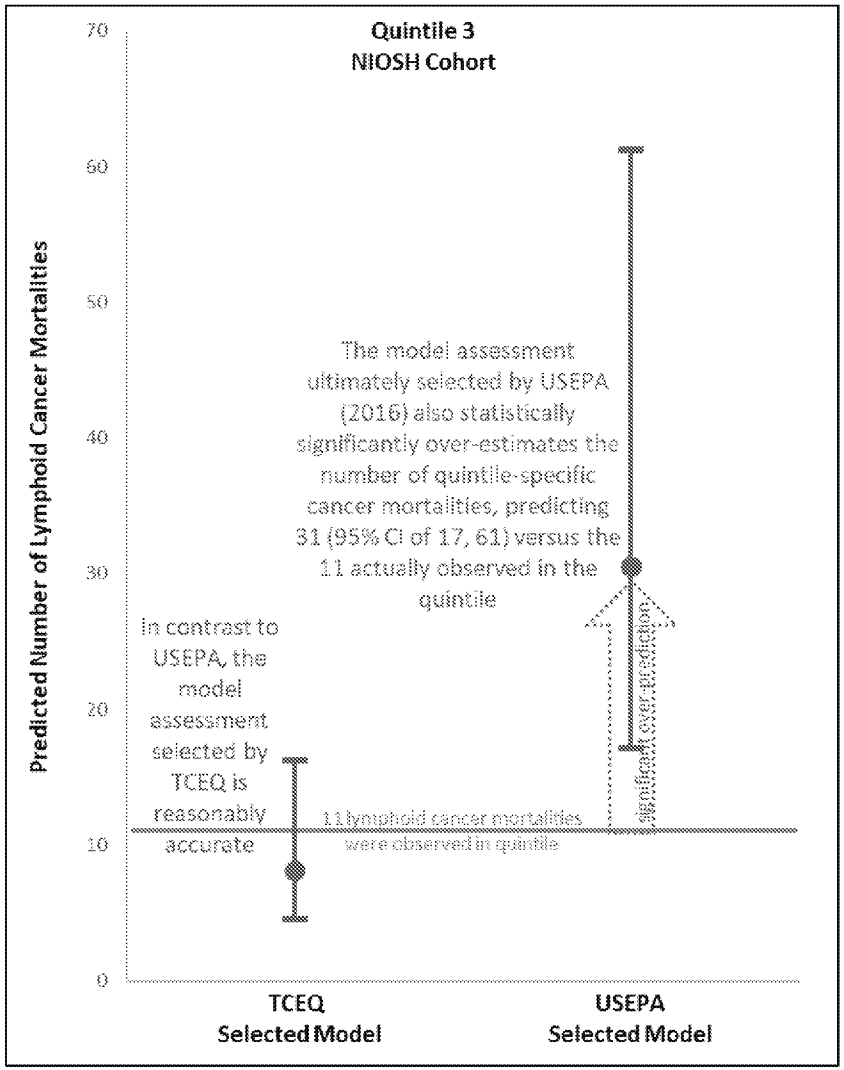
Model Predictions of the Key Data

- Likewise, for each exposure quintile of the key NIOSH worker study, *USEPA's selected model assessment statistically significantly over-predicts lymphoid cancers* while TCEQ's model is relatively accurate…



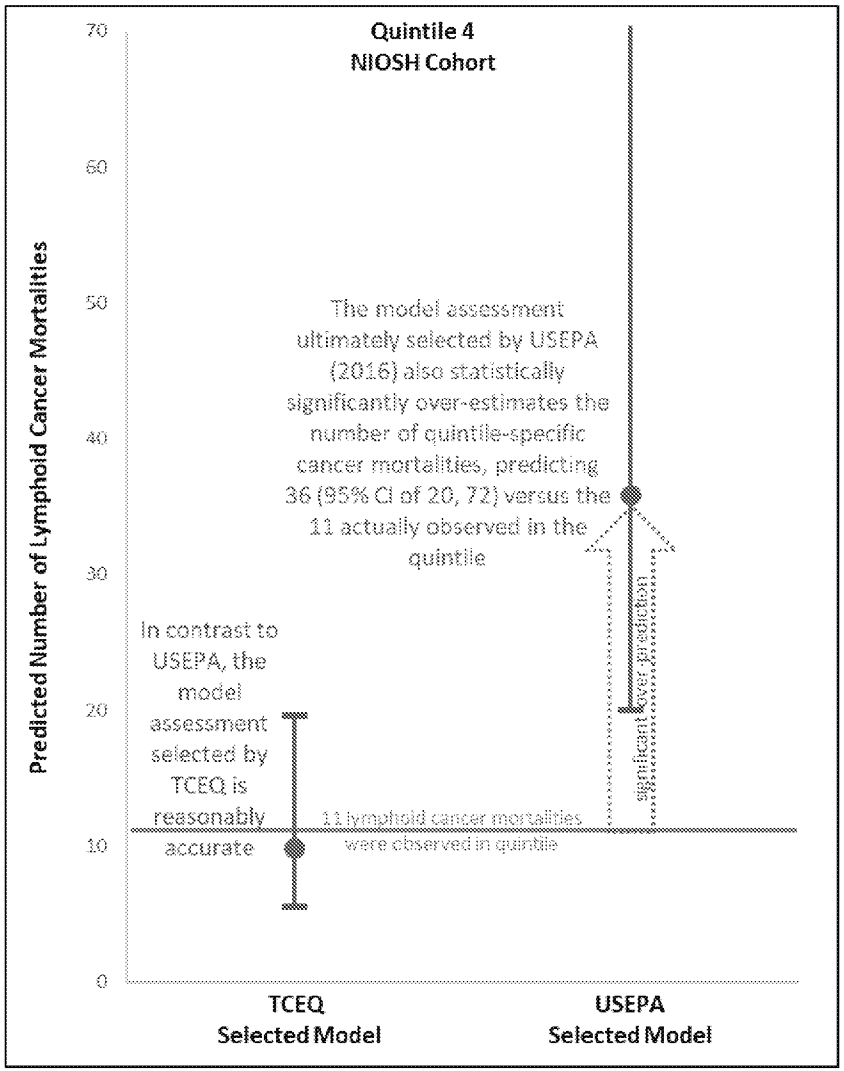
Model Predictions of the Key Data

- For the next exposure quintile of the key NIOSH study, *USEPA's selected model assessment again statistically significantly over-predicts lymphoid cancers* while TCEQ's model is relatively accurate…



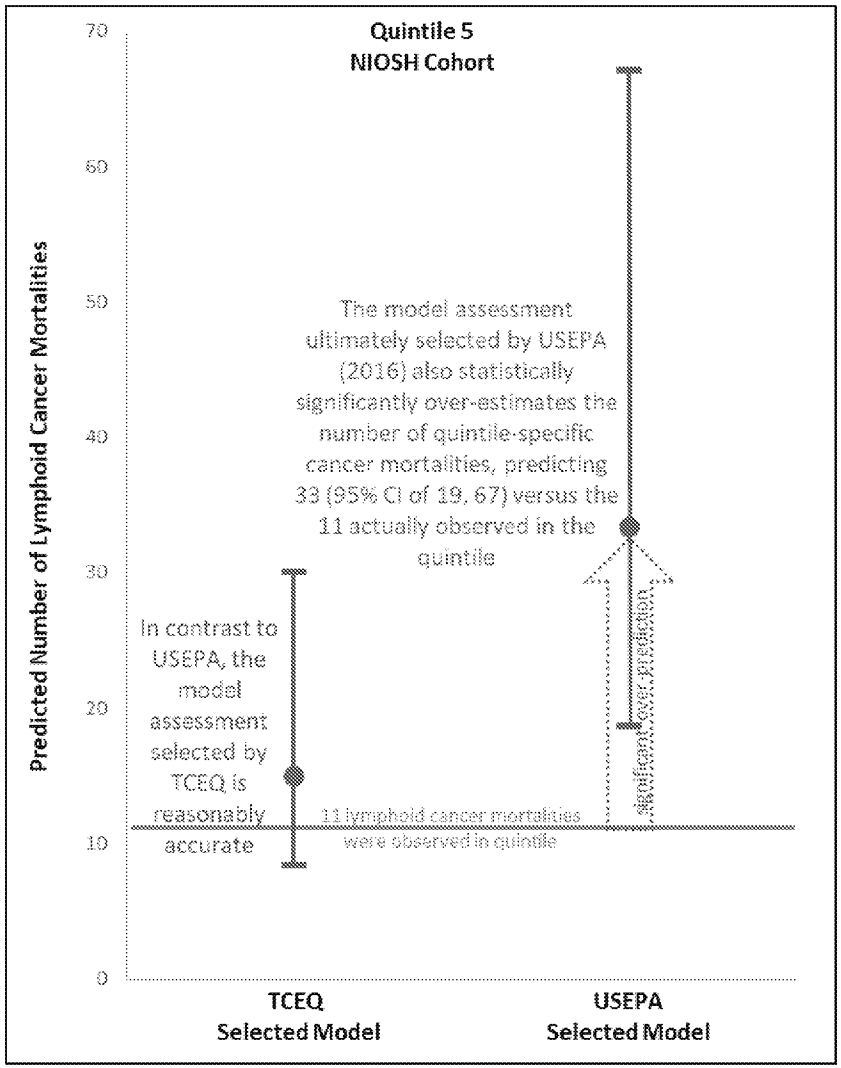
Model Predictions of the Key Data

- Again, for the next exposure quintile of the key NIOSH dataset, *USEPA's selected model assessment statistically significantly over-predicts lymphoid cancers* while TCEQ's model is relatively accurate…



Model Predictions of the Key Data

- Finally, for the last exposure quintile of the key NIOSH study, *USEPA's selected model assessment also statistically significantly over-predicts lymphoid cancers* while TCEQ's model is relatively accurate…



Model Predictions of the Key Data

- Maximum likelihood estimate (MLE) model predictions follow a very similar pattern, with *USEPA's overall supra-linear model statistically significantly over-estimating lymphoid cancers* for the NIOSH cohort as a whole and for all but one exposure quintile.

- By contrast, the MLE for TCEQ's model neither significantly over- or under-estimates lymphoid cancers but remains relatively accurate.

Model Predictions of the Key Data

- *Bottom Line*: The standard model used by the TCEQ is demonstrably superior (i.e., Cox proportional hazards model).
  - TCEQ's selected model assessment is *consistent with the MOA* and *accurately describes the key worker cohort data*.
  - USEPA's unconventional model (admittedly not supported by mechanistic data) *statistically significantly over-predicts the key underlying data* yet is still being used to estimate EtO risk across the nation.

Model Predictions of Background

- In addition to USEPA's selected model over-predicting lymphoid cancer for the workers it was supposed to accurately describe, *the USEPA URF* being used to estimate EtO risk around the country *over-estimates background lymphoid cancer incidence in the general population*.

Model Predictions of Background

- Use of the EtO air concentration corresponding to the mean of normal endogenous background levels in the unexposed population (1.9 ppb) in conjunction with the USEPA (2016) age-dependent adjustment factor (ADAF)-adjusted URF for lymphoid cancer (7.1E-03 per ppb) suggests a background incidence of ≈1.35% in nonsmokers due to endogenous EtO alone.
- Remarkably, this would be almost half (46%) of the lymphoid cancer background incidence of 3% (p. 4-95 of USEPA 2016).

Model Predictions of Background

- However, background levels in the smoking population must also be considered.
- Use of the EtO air concentration corresponding to the mean background in adult smokers (18.8 ppb) along with that for nonsmokers (1.9 ppb) for the first 18 years provides a lifetime smoker background level corresponding to ≈15.2 ppb EtO, for which USEPA's lymphoid cancer URF suggests an incidence of lymphoid cancer in smokers of ≈11% due to EtO alone (note: even with EtO and numerous other carcinogens in tobacco smoke, evidence in smokers is not sufficient to infer a causal relationship with lymphoid cancer [or breast cancer] per USDHHS 2014).

Model Predictions of Background

- Weighting the URF-estimated lymphoid cancer incidence for smokers (11%) at ≈25% of the population (for 1985-2005, consistent with the USEPA 15-year exposure lag period) with that for nonsmokers (1.35%) results in a current population estimate of ≈3.7% due to background EtO levels alone.

Model Predictions of Background

- This USEPA URF-predicted population background is higher than the actual lymphoid cancer background incidence of 3% cited by USEPA, and considers background EtO alone (e.g., without contributions from EtO or ethylene in ambient air, known chemical leukemogens, or other risks factors), indicative of a *scientifically unreasonable* URF.

- By contrast, the TCEQ URF predicts a lymphoid cancer background rate well within actual background, indicative of a *scientifically reasonable* and *biologically plausible* URF that in addition to background levels in nonsmokers and smokers, allows for contributions from EtO in ambient air, other chemical leukemogens, and other risk factors.

Model Predictions of Background

- *Bottom Line*: As with the key worker population, while USEPA's unconventional model over-predicts lymphoid cancer in the general population (based on background EtO alone, without contributions from EtO or ethylene in ambient air, known chemical leukemogens, or other risks factors), the standard model selected by the TCEQ does not.
- Yet again, the standard model used by the TCEQ is demonstrated to be more realistic.

Key Epidemiological Findings

- Workers in the key NIOSH cohort were exposed to EtO concentrations ≈15,000-32,000,000 times higher than the typical environmental levels cited by USEPA.

- With such high exposures for > 17,000 workers, if EtO were as potent of a carcinogenic as USEPA's selected dose-response assessment suggests, then human data alone would be expected to sufficient to categorize EtO as *carcinogenic to humans*, but are not as even higher dose animal study results must be included in the carcinogenic weight-of-evidence (note: no cancer increase for highly-exposed UCC cohort thru 2013).

Key Epidemiological Findings

- *Food for thought*: benzene is classified as carcinogenic to humans based on human data alone (e.g., IARC 2018), even though…
  - The USEPA benzene URF range (2.2-7.8E-06 per µg/m^3) suggests three orders of magnitude (1,000×) lower carcinogenic potency than EtO, and when
  - All benzene worker annual exposure means in the small key Pliofilm worker cohort are adjusted for this presumed potency difference (e.g., 4-137 ppm/1,000 = 0.004-0.137 ppm; Kipen et al. 1989), they fall well below the EtO worker exposure means in the much larger key NIOSH worker cohort (3.5-4.6 ppm; Hornung et al. 1994).
- So human data alone are sufficient to conclude benzene is a known human carcinogen despite *lower* carcinogenic potency-adjusted exposure in a *smaller* key study? Yes.

Key Epidemiological Findings

- *Looked at a different way*: ≥40 ppm-years of occupational benzene exposure is where USEPA (1998) states there is fair confidence that the risk of leukemia increases based on the small key Pliofilm worker cohort and other studies, which is actually *less than or similar to* doses of EtO that appear carcinogenic in a much larger NIOSH cohort (e.g., DSD Table 4: ≥70,223 ppm-days/250 occupational days per year = ≥281 ppm-years; DSD Table 5: ≥13,500 ppm-days/250 occupational days per year = ≥54 ppm-years when lagged 15 years).

- This simple carcinogenic dose comparison example does *not* suggest that EtO is 1,000× more carcinogenic than benzene; rather, it suggests an EtO carcinogenic potency perhaps similar to or somewhat less than that of benzene.

- Consistent with this, the TCEQ's modeled 1 in 100,000 excess risk air concentrations happen to be similar: 1.4 ppb benzene, 2 ppb EtO (ADAF-adjusted; 4 ppb unadjusted).

Key Epidemiological Findings

- Moreover, the TCEQ has shown that if EtO were as potent of a carcinogenic as USEPA's selected dose-response assessment suggests, then statistically significant increases in lymphoid cancer would have occurred in all exposure quintiles of the NIOSH study, including the lowest.
- But in fact, this did not occur, demonstrating an overly-predictive model and that EtO is not as potent of a carcinogen as USEPA's unconventional and unpredictive dose-response modeling suggests.

Endogenous vs. Carcinogenic Doses

- Relative to endogenous doses, carcinogenic doses in the NIOSH cohort are orders of magnitude higher...

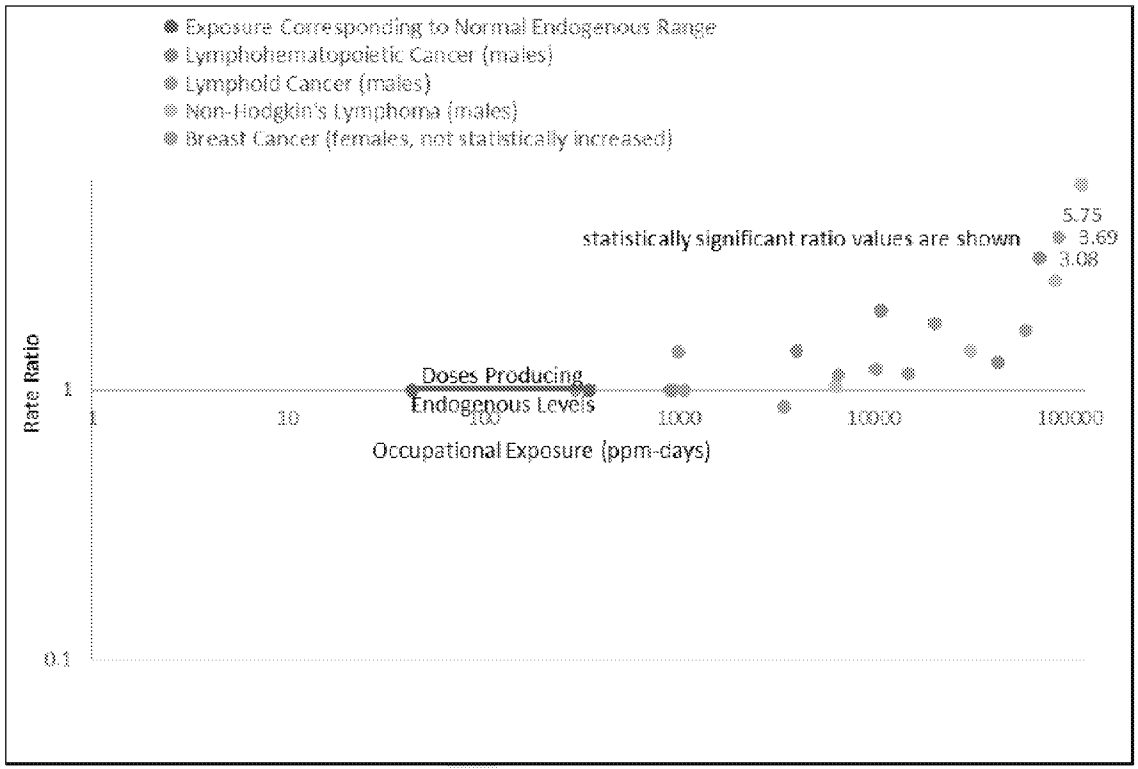
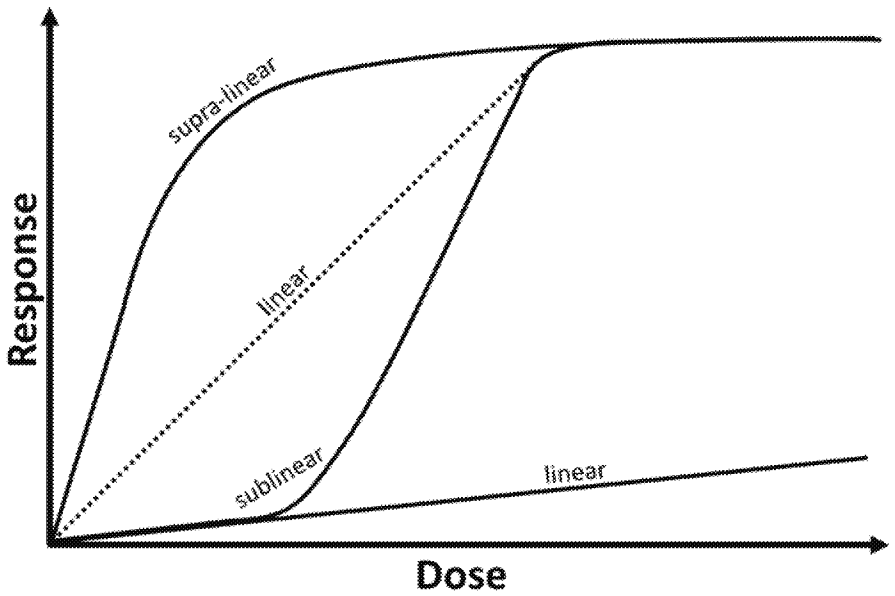


Figure 3: Occupational Exposures Corresponding to Normal Background Endogenous Levels of EtO versus Exposures Associated with Statistically Significant Increases in Critical Cancer Endpoints in the NIOSH Cohort - Log Scale

Endogenous vs. Carcinogenic Doses

- USEPA (2016) indicated that it is "highly plausible that the dose-response relationship over the endogenous range is *sublinear*"…



Endogenous vs. Carcinogenic Doses

- ...but then *USEPA applied remarkably steep <u>supra-linear</u> model low-dose slopes for cancer in the very region where they expect <u>sublinearity</u>...*

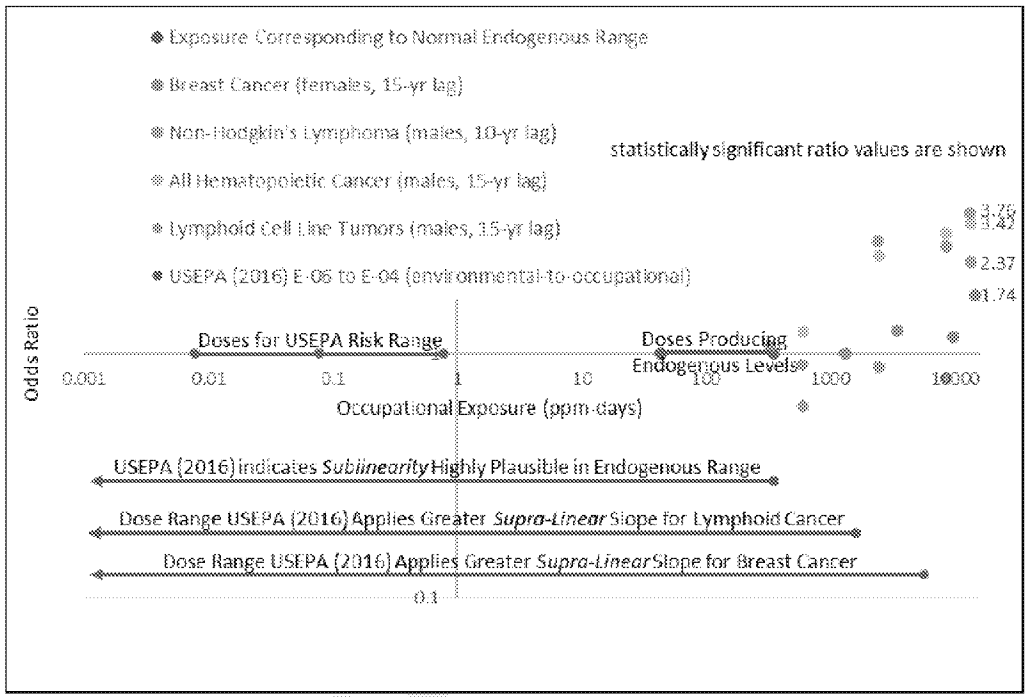


Figure 7: Occupational Exposures Corresponding to USEPA Risk-Based Doses and Normal Background Endogenous Levels of EtO versus Lagged Exposures Associated with Statistically Significant Increases in Critical Cancer Endpoints in the NIOSH Cohort - Log Scale

Endogenous vs. Carcinogenic Doses

- It bears repeating that the consequence is that the EtO air concentration at even the maximum acceptable excess risk (0.01 ppb at 1E-04 risk) is almost 40 times lower than that corresponding to the 1st percentile of normal endogenous background levels.

- Put another way, the USEPA considers EtO air concentrations corresponding to more than ≈0.5% percent of mean normal endogenous in nonsmokers to be associated with unacceptable risk *applying an overall supra-linear model to the very region where they expect sublinearity*.

Model Fit Criteria

- Neither USEPA nor TCEQ can cite mechanistic data for EtO (the primary consideration) that support use of a supra-linear model, particularly over the low-dose region where both agencies expect sublinearity.

- Two important overarching issues with USEPA's and TCEQ's consideration of model fit are the:
  1. Statistical optimization of "knot" values for USEPA's two-piece spline modeling; and
  2. Visual misrepresentation of model fit by USEPA (2016) Figures 4-3 and 4-8.

Model Fit Criteria

- For the statistical optimization of "knot" values, splines were "fit" to the EtO cancer exposure-response data using different knot values.
- The knot was generally selected by choosing the one that resulted in the best (i.e., largest) model likelihood.
- Thus, the "knot" was an iteratively fit model parameter and not simply "preselected".

Model Fit Criteria

- Accordingly, the knot values, being statistically estimated/optimized based on the NIOSH data, *clearly do not conform* to the USEPA SAB's notion of fixed model parameters *not estimated from the data* in the interest of parsimony (see p. 12 of SAB 2015).

- It is clearly technically incorrect to statistically estimate/optimize a model parameter upstream of a final model and then *not count the fitted parameter* as an estimated (k) parameter, as was done in USEPA (2016) for the linear two-piece spline model.

Model Fit Criteria

- As USEPA (2016) did not account for statistically estimating the optimized knot value, the degrees of freedom (*df*) were inappropriately enlarged for the spline models, which resulted in an:
  - *Inappropriately decreased p-value for adequate statistical fit by spline models*, incorrectly implying that the linear two-piece spline model for lymphoid cancer fit the data statistically better than other models; and
  - *Inappropriately decreased Akaike information criteria (AIC) for spline models*, which did not allow for an appropriate comparison of model fit among models for either lymphoid cancer or breast cancer incidence.

Model Fit Criteria

- Correct p-values indicate that the two-piece spline models *do not* explain the variability in the data statistically significantly better than the null model (zero slope) or the standard Cox regression model used by TCEQ and demonstrated to predict lymphoid cancers in the NIOSH cohort more accurately.

- Similarly, correct AIC values do not support use of USEPA's unconventional linear two-piece spline model over the standard Cox regression model that more accurately predicts lymphoid cancers for the cohort.

Model Fit Criteria

- Since USEPA (2016) also relied on visual fit, it must be noted that no true visual comparison of model fit to the data can be made based on Figures 4-3 and 4-8 of USEPA (2016) since *the data shown are not the data to which the models shown were fit*.

- The actual data underlying model fits shown are the *individual data*, not the less refined *categorical data* shown in the figures, which consequently do not show model fit to the modelled data at all.

Model Fit Criteria

- Even ignoring more deterministic considerations (e.g., MOA, biological plausibility, predictiveness), objective examination of the underlying data reveals no readily apparent superior visual fit…
- In fact, other equally visually plausible lines could be drawn.

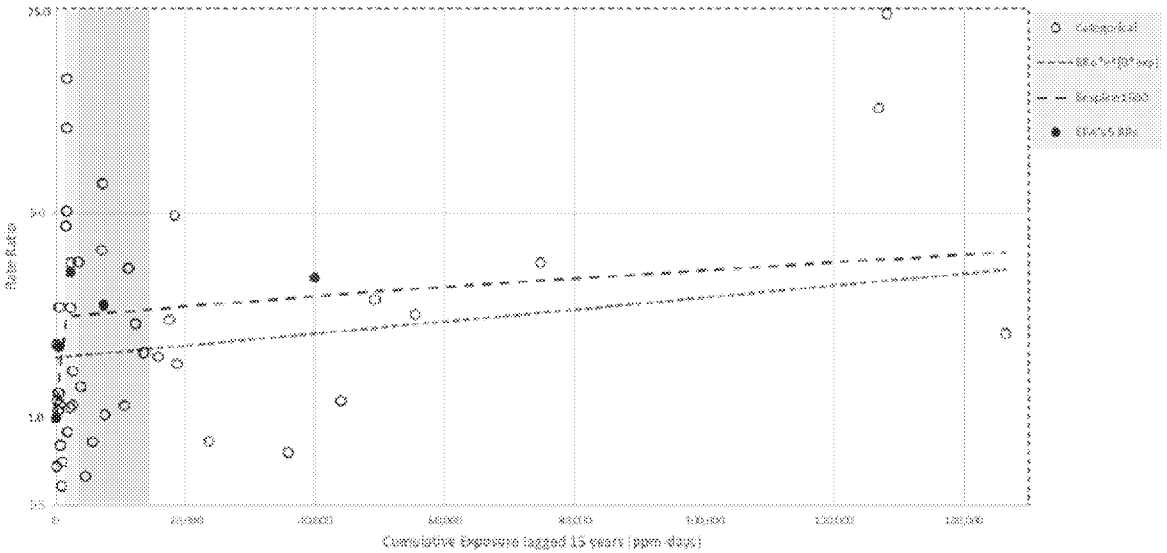


Figure 22: Lymphoid Cancer Death Categorical RRs and the Cox Proportional Hazards and Two-Piece Spline ("knot" at 1,600 ppm × days) Fitted Models for 15-Year Lagged Occupational Doses ≤150,000 ppm × days (NIOSH cohort)

Model Fit Criteria

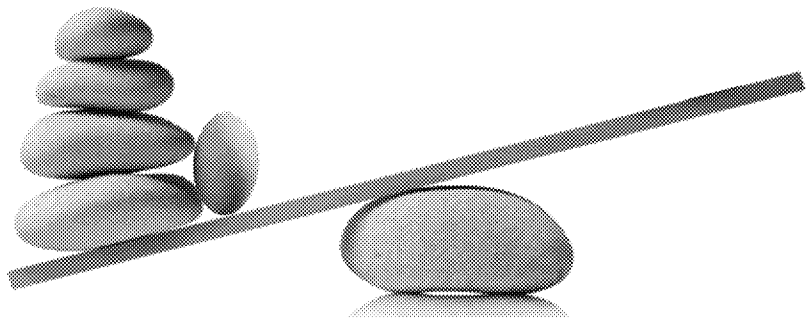
- Thus, consistent with relevant considerations based on: (1) MOA, (2) model predictions for lymphoid cancer in the key NIOSH cohort, (3) carcinogenic dose data, (4) data on normal endogenous levels, and (5) reality checks on population background incidence…

  none of these standard model fit considerations support USEPA's deviation from more standard, conventional dose-response models (e.g., the Cox proportional hazards model as used by the TCEQ), even if all else were equal.

In Summary

Supported by?	TCEQ Model Assessment	USEPA Model Assessment
MOA Information	Yes ✓	No
Statistically Accurate Model Predictions of the NIOSH Cancer Data	Yes ✓	No
Reality Checks on Population Background Incidence	Yes ✓	No
Endogenous Level Data/ Biological Plausibility	Yes ✓	No
Standard Modeling Approach		

The Weight of Evidence



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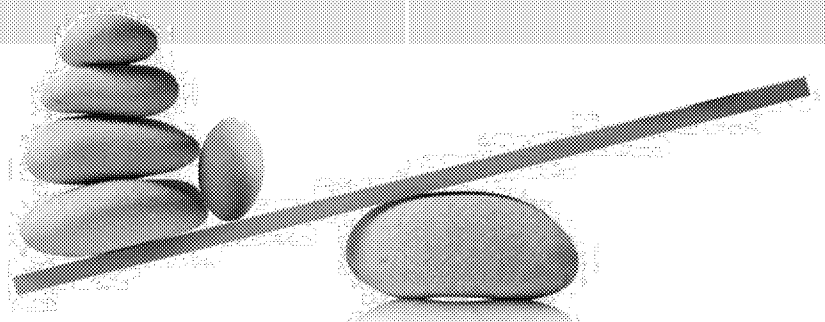

In Summary

- TCEQ's standard dose-response model is demonstrated to be accurate, while USEPA's unconventional model is demonstrated to be inaccurate for the:
  - Key worker lymphoid cancer data that drives the URF; and the
  - US population at large.

- TCEQ's dose-response model is supported by the MOA while neither agency can cite MOA data supportive of USEPA's overall supra-linear model.

In Summary

- TCEQ's model fit criteria are correctly calculated whereas USEPA's criteria are demonstrably incorrectly calculated.
- USEPA used an overall *supra-linear* dose-response to extrapolate over and below the endogenous region where the agency says they actually expect *sublinearity*.
- As a result, USEPA's acceptable air concentrations are at doses orders of magnitude below normal levels of EtO in the body, whereas the TCEQ's acceptable air concentration (2 ppb; ADAF-adjusted) is not.

In Summary

- So why is bringing all this to light important? What difference does using best available science make?

Excess Risk Level	TCEQ (ppt)	USEPA (ppt)
1 in 10,000	20,000	10
1 in 100,000	2,000	1
1 in 1,000,000	200	0.1

Sound Science is Needed for EtO

Letter Health Consultation

"Evaluation of Potential Health Impacts from Ethylene Oxide Emissions"

STERIGENICS INTERNATIONAL, INC.

WILLOWBROOK, ILLINOIS

Table 1. Statistical distribution of EtO modeling*

Statistics	Modeled 1-hour (µg/m³)	Modeled 8-hour (µg/m³)	Modeled 5-year (µg/m³)
Minimum	2.17	1.02	0.03
25th Percentile	4.62	2.26	0.09
50th Percentile	9.72	4.07	0.17
75th Percentile	18.88	7.29	0.31
90th Percentile	33.90	12.62	0.57
95th Percentile	45.22	18.83	0.91
99th Percentile	134.73	61.39	2.97
Maximum	249.77	123.89	13.32
Mean	15.75	6.72	0.32
Geometric Mean	10.13	4.41	0.18

**N= 882 modeled receptors*

Table 3. Range of measured and modeled EtO concentrations: U.S. EPA Cancer Risk Estimates

Statistics	Modeled 5-year (µg/m³)	Modeled cancer risk range	12-hour samples (µg/m³)	Measured cancer risk range*
Minimum	0.03	1.3E-04	0.16	7.9E-04
Maximum	13.32	6.7E-02	4.34	4.5E-02
Mean	0.32	1.6E-03	1.04	1.4E-02
Geometric Mean	0.18	9.1E-04	0.61	7.7E-03

*Cancer risk was calculated to estimate what long term exposures to the 12-hour concentration could look like if sustained long term and does not represent actual exposures.

> upper end of USEPA acceptable excess risk range (1E-06 to 1E-04)

- Based on USEPA (2016), ATSDR (2018) concludes, "If measured and modeled data represent typical EtO ambient concentrations in ambient air, an *elevated cancer risk* exists for residents and off-site workers in the Willowbrook community surrounding the Sterigenics facility. These elevated risks present a ***public health hazard*** to these populations."

Sound Science is Now Available for EtO

Table 1. Statistical distribution of EtO modeling*

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Maximum	249.77	123.89	13.32
Mean	15.75	6.72	0.32
Geometric Mean	10.13	4.41	0.18

N= 882 modeled receptors

- However, USEPA's 2016 selected model assessment and EtO inhalation URF are not scientifically defensible.
- By contrast, the TCEQ's assessment and URF are supported by relevant scientific considerations and the weight of scientific evidence.
- Except for the maximum, all 5-year modeled EtO air concentrations are below TCEQ's lifetime ADAF-adjusted 1 in 100,000 excess risk air concentration (2 ppb or 4 µg/m³).
- Moreover, the entire 5-year modeled distribution is well below the air concentration at the upper end of USEPA' s acceptable excess risk range based on TCEQ's more scientifically supported assessment (i.e., 40 µg/m³ at a lifetime excess risk of 1 in 10,000).

Sound Science is Needed for EtO

In FDA's October 25, 2019 statement:

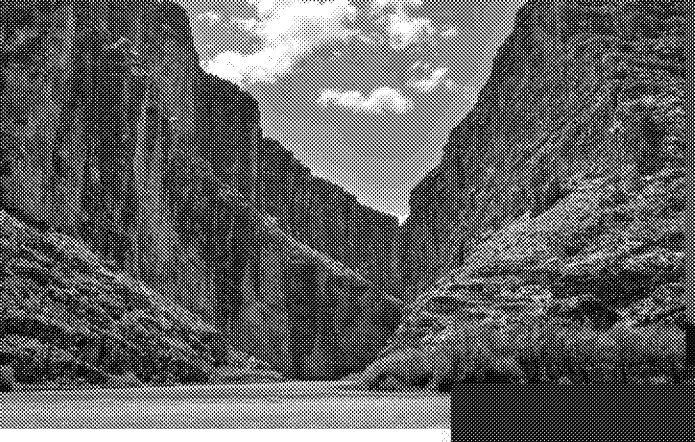
- Sterilization facility closures could affect the availability of some sterile medical devices used by health care delivery organizations and patients.
- In light of the possibility of continued EtO sterilization facility closures, FDA is again alerting the public to growing concerns about the future availability of sterile medical devices and impending medical device shortages.
- More than 20 billion devices sold in the U.S. every year are sterilized with EtO, accounting for approximately 50% of devices that require sterilization.
- Without adequate availability of EtO sterilization, we anticipate a national shortage of these devices and other critical devices.
- In short: this method is critical to our health care system and to the continued availability of safe, effective and high-quality medical devices.
- The impact resulting from closure of facilities will be difficult to reverse, and ultimately could result in years of spot or nationwide shortages of critical medical devices, which could compromise patient care.

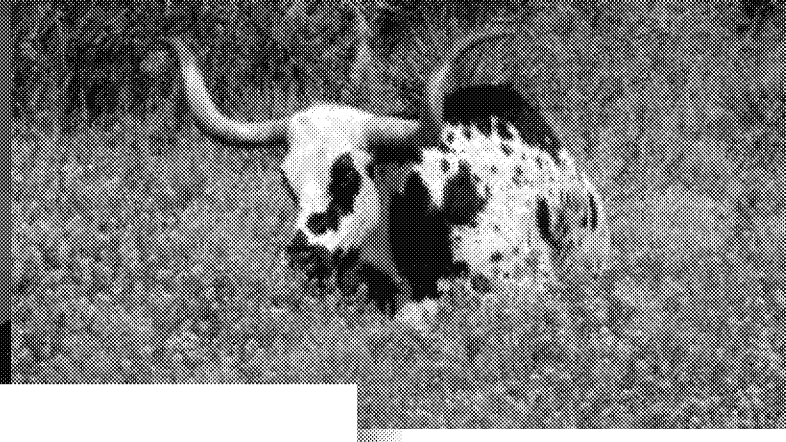
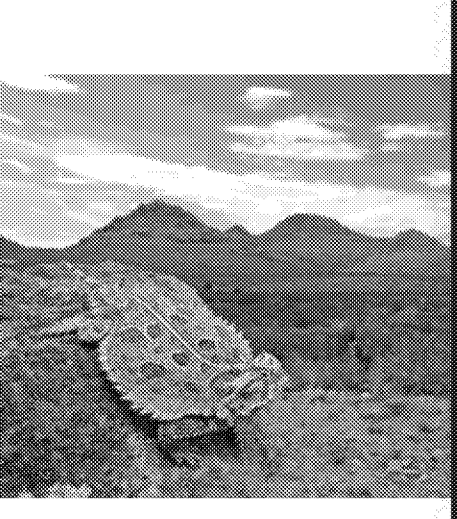
In Conclusion

- The TCEQ's goal is to use the best available science in deriving toxicity factors and making regulatory decisions.
- All relevant information evaluated by the TCEQ has indicated that USEPA's selected dose-response assessment and URF are significantly over-predictive, biologically implausible, and scientifically unsupportable.
- By contrast, the same scientific information fully supports the TCEQ's dose-response assessment of the carcinogenicity of EtO.

In Conclusion

- This and similar assessments have important regulatory, public health, and risk assessment/communication implications (e.g., whether typical environmental exposures and those near sterilization facilities represent realistic health concerns/hazards or not).
- Consequently, the TCEQ encourages you to read the agency's DSD for EtO as well as all relevant studies in order to formulate your own independent and objective conclusions on the assessment.



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